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Notes on the Pandemic #3

March 30, 2020

Dear DCI Community,

I hope you are all doing well. I was wonderful to have so many of you our DCI Community Town Hall Zoom meeting on Wednesday, March 25th. It was great to see so many of you and we look forward to more opportunities. In fact, we are planning another Zoom event on Monday, April 6th likely at 3pm Pacific Coast time – since that will provide the best global accessibility. Details will follow shortly.

For all of us it is ever more surrealistic to be gazing around the world from our various shelter in place (really at home) locations. On the one hand, we are all engaged in very different ways with family, friends and our local communities, and many of now know individuals who have already been impacted by SARS-CoV2. And of course, for some this has been a frightening and even horrifying experience. That said, I am unwavering in the belief that what is so challenging now will, in time, recede into the distance. I hope that when it does, we will have a greater appreciation of how the current realities relate to our future lives. There is no doubt that epidemics and pandemics will return –as they have always been part of recorded human history.

First, a few lessons in microbiology and immunology. Although we may not wish to dwell on this fact, the reality is that each of us is comprised of as many or even more microbes than human cells. In fact, there are about a hundred trillion microbes on or in us – the great majority in our GI tract but also in other body cavities and orifices and of course on our skin (which comprises a huge surface area). Our 2019 Fellows will learn more about the Microbiome on Wednesday, April 1st from Justin Sonnenberg (<https://sonnenburglab.stanford.edu/>) who together with his wife Erica co-authored a highly readable book entitled “*The Good Gut*” that was published in 2015. For the most part we have a collaborative relationship with all of these microbes, and we recognize that many microbes do good things for our bodies, whereas others can promote inflammation and disease. The balance of power between us and our microbes (including the ones we acquire from sources outside of our body) is mediated by our immune system – which includes our innate defenses that operate by pattern recognition and provide the first lines of defense that is then followed by our acquired immune system that provides longer term protection. The acquired immune system provides immunity against most microorganisms (including the ones we are immunized against) by what is called humoral immune system that includes specialized proteins in blood, body fluids and tissues that is largely mediated by antibodies; there are several types of these important molecules. In addition to humoral immunity, there is cellular immunity (especially through lymphocytes and other specialized cells including dendritic cells), which helps with long term defense against microorganisms as well as other foreign invaders. In addition, to humoral and cellular immunity there are also front-line cells called phagocytes (there are several types) that help kill certain microorganisms and the

inflammatory response they produce can be seen as pus or the inflammation associated with cellulitis as visible examples.

When the immune system functions normally, it keeps things in balance. However, if the immune system becomes compromised (e.g., from cancer therapy that reduces immune defenses or from congenital immunodeficiencies and acquired immunodeficiencies -like HIV/AIDS) even otherwise harmless germs can become dangerous and result in severe infection. Or as is the case with SARS-Cov2, a new organism which is often either a mutated one or one that arises from another species – called a zoonosis) can cause more widespread infection because nearly all people are immune-naïve to the new organisms. Of note, SARS-Cov2 is both a mutant as well as zoonosis – meaning that it was transmitted to a human from an animal and along the way (in either the animal or in the human) further mutated so that it could lead to human-to-human transmission. As you know, it is because of these mutations in this unique coronavirus, that bears considerable genetic similarity to the SARS virus that I discussed in earlier letters, that SARS-CoV2 has resulted in this new disease called Covid19. I know we are all spending a lot of time focused on COVID, but I thought it might be helpful (or least interesting), it is also important to put SARS-Cov2 into a historical perspective.

First microorganisms antedate animal species in the evolutionary chain. It is estimated that there are about a trillion microorganisms on earth living at all extremes of the global environment - from the hottest to the coldest extremes. Most of them have not even been identified to date. There are millions of different microorganisms comprising the human microbiome and, as noted above, in the aggregate, they number more than 100 trillion members of our body mass.

There are several major categories of microorganisms, the most common being bacteria, most of which are free living but some live inside of host cells. Overall, there are 7 different classes of microbes, several of which inhabit humans in various ways: bacteria, archaea, fungi, protozoa, viruses and multicellular animal parasites like helminths (for example hookworm). Of these microorganisms, viruses are among the smallest and simplest and cannot live to reproduce on their own – they require entry into a cell where they hijack the genetic machinery to replicate. That is the case with SARS-Cov2, where the major target cell is in the upper and lower respiratory track. There is also a unique infectious agent (really a protein) called prions that can be the cause of rare neurodegenerative diseases – but that is a story for another time.

Most infections are local events, but some microorganisms have the capacity to cause wide contagion and to spread geographically. For example, the microbes most responsible for epidemics and pandemics (see below) include viruses (i.e., smallpox, influenza, polio, HIV/AIDS, and Ebola) whereas bacteria (the cause of plague, syphilis, tuberculosis and cholera) and parasites (the cause of malaria) are among the most notable infectious agents. Of course, there are many other highly contagious human infectious disorders, some even more contagious than SARS-CoV2 (measles being the most notable) and many of these are associated with milder and less lethal infections. For example, the four coronaviruses that cause about 15% of human “colds” would fall into this category. Of course, we now need to include SARS (which caused a limited pandemic) and SARS-CoV2 as two additional viruses capable of causing pandemics.

Over the long arc of history, there have been regular epidemics and less frequent pandemics. According to the CDC and WHO an epidemic refers to a disease that affects many individuals at the same time and that spreads within a region or community where it is not normally prevalent. A pandemic is an extension of this, an refers to an epidemic that has spread more widely to involve an entire country, continent or, as in the case of SARS-CoV2, the world. You will recall that the WHO did not declare the current coronavirus epidemic a “pandemic” until March 11th when it involved some 114 countries. This was some three months after the first cases had been described in Wuhan, China.

While the current pandemic seems entirely new, there have been many other pandemics during human history. However the current SARS-CoV2 pandemic has unfolded incredibly rapidly because of a number of converging factors: it is a unique new organism to which pre-existing immunity to modify or infectivity is largely absent (although the mild infection in children awaits an explanation), the rapid spread across all geographic borders because of the international travel and the increasing density of cities where the majority of people now live are all contributing to this pandemic. So too is the fact that many individuals have subclinical or even asymptomatic infection and yet are able to transmit the virus, which has allowed spread to occur because of a lack of recognition of prevalence, coupled with the lack of organized public health measures for containment that were hindered by a panoply of errors, in particular the lack of testing which in many countries, including the US, led to delays and a resultant exponential spread of the virus, including to highly vulnerable communities. As I noted in my prior letter, this was not universally true and some countries, most notably Taiwan, was prepared and enacted a highly effective response that protected its population in ways that we wish had happened in the US – and which I hope will be the case in the future.

As noted above, not all pandemics throughout history are due to viruses. The first recorded pandemic occurred in 480 BCE in Athens during the Peloponnesian War and was caused by typhoid (a bacteria that had human-human transmission). Of course, the footprint of the world was smaller at that time. In 165 CE the so-called Antioch Plague spread through the Roman Empire and seems to be the first appearance of smallpox (a virus).

Most of us think about pandemics in relation to “Bubonic Plague” or the Black Death, which is caused by a bacteria called *Yersinia pestis* that is spread by fleas from infected rodents. The plague came in cycles and had led to the death of 20% of the population of London in 1665. The introduction of new organisms like smallpox, measles and plague had a devastating impact on the new world beginning in 1492 and ultimately led to the deaths of 56 million Native Americans in the 16th and 17th centuries as well as the destruction of the Aztec Empire in 1520 by smallpox. This is one of the topics in Jared Diamond’s *Guns, Germs and Steel* that I reference below. Cholera has also contributed to major pandemics in Asia, especially China but also caused major disease in Europe, including the famous outbreak in London (see below).

The comparative reference point for the current SARS-Cov2 pandemic is the 1918 Influenza Pandemic that resulted in some 50 million deaths and which occurred in two waves, which is one of the concerns for the current coronavirus infection.

I share these examples to simply provide context and comparison. The association between emerging infections and the transformation of society has been an integral facet of the story of civilization. We are living through a new chapter of this story, but it is not the end. There will be others, some of which will be the result of climate change that will impact microorganisms and in some cases the vectors that transmit them.

As many of you know, I have been interested in the association of infection and history for most of my life, beginning as a teenager when I read Paul De Kruif's *The Microbe Hunters* (published 1926 – yes that was before I was born) and which is what led me to a career in medicine and research. For those of you might want to learn more about this interesting area that lies at the nexus between science, policy, public health, social behavior and history, here are some interesting books, some of which you may have read but others that might be of interest – perhaps ever more now because of what you are witnessing.

- Jared Diamond. **Guns, Germs and Steel** (1997) – *this is one of the classics of how infectious agents are even more powerful than weapons in impacting immune naïve communities.*
- William McNeill. **Plagues and People** (1976) – *a scholarly review by a noted historian.*
- Laurie Garrett. **The Coming Plague. Newly Emerging Diseases in a World Out of Balance** (1994) – *interesting but a bit sensational in parts.*
- Frank Snowden. **Epidemics and Society** (2019)
- Steven Johnson. **The Ghost Map. The Story of London's Most Terrifying Epidemic and How it Changed the Modern World** (2006) – *reads like a novel.*
- Gina Kolata. **Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It.** (1999) – *from the well-known science writer for the New York Times.*
- Frank Ryan. **The Forgotten Plague** (1993) – *story of tuberculosis and the search for its treatments.*
- David Oshinsky. **Polio. An American Story** (2005) – *winner of the Pulitzer Prize.*

Of course, this is just a sampling and is all non-fiction. As you know there is an extraordinary array of incredible fiction and philosophy books that are sometimes even more remarkable to read. I have no doubt that there will be a number of books about SARS-Cov2 and COVID19 – that will include non-fiction and fiction – and some which blurs the boundaries between them (as we are even witnessing today).

What is new in the epidemiology and course of infection?

Since my first communication some of our understanding about the clinical course of COVID has evolved with additional data from the US (where, as I write this report today, there are over 745,000 cases globally and 144,672 cases the US, the highest number in the world) which almost certainly an underestimate. For those who develop symptoms, the major manifestations include fever (83-98%), cough (46-82%), myalgia (11-44%) and shortness of breath (31%). The incubation period is approximately 14 days with the median at 5.1 days. What is notable is that asymptomatic cases are clearly defined and associated with high viral loads (the amount of virus

in the nose or airway) prior to onset of symptoms. There are estimates of virus shedding (as measured by PCR) up to a week prior to onset of symptoms. It is also notable that in China, where pulmonary CT scans were performed, 71% had some abnormalities prior to the onset of any pulmonary symptoms. Of course, this is why most communities have much more virus in the community than indicated by those who have been tested, most of whom who have been symptomatic. It is also of note that infection involves young adults and while most are asymptomatic, children as well.

With more testing and comparative data, including from the ongoing Influenza Surveillance in Seattle, it has been demonstrated that positive diagnosis can be achieved from the simpler to do nasal swabs compared with nasopharyngeal swabs, and that patient sampling is as effective as that done by healthcare providers. Based on increasing epidemiologic data it appears that the R_0 (how contagious an infectious disease is) for SARS-CoV2 (as a measure of infectivity or contagiousness) is likely between 1.8-2.2. By comparison, the R_0 for SARS is 4 and both of these are less than the most contagious viruses, mumps with an R_0 of 10 and measles with an R_0 of 18. These latter infections involve aerosolization in addition to air droplets (which appears to be the case for SARS-CoV2). It also seems clear that transmission is associated with the virus load and that is highest with continued exposure, which is why household exposure or that in contained places (e.g., cruise ships, nursing homes) increase the likelihood of transmission and infection.

Once infected, individuals of all ages (albeit much less so in children) can manifest symptoms and go on to more serious disease. There are basically four phases: the incubation phase that ranges up to 14 days, with a median of 5.1 days, prior to the onset of symptoms. For those who develop symptoms, they can range from mild to severe, with the most serious respiratory symptoms occurring during the second week when shortness of breath (dyspnea), rapid breathing (tachypnea) and low blood oxygen (hypoxemia) are manifest. Some of these individuals go on to respiratory failure due to ARDS, which is really hyperinflammation syndrome that is sometimes called a “cytokine storm” because of all the inflammatory mediators that are produced that adversely impact the lungs. There are now also reports of heart damage (so called cardiomyopathy) that impacts cardiac function that is associated with COVID. In some cases, heart failure caused death in individuals who appeared to be stabilizing from their pulmonary infections. Of course, this all sounds frightening and I want to underscore that case fatality is likely lower than was initially reported from China but there is a range from 1.3% to 14%. While deaths can occur in all ages (including rare cases in young children), the highest risk group remains older individuals, including those in their 60s but especially in the 70s, 80s and above. In addition to age, an impacting all ages, are other co-morbidities or chronic disorders including immunocompromised individuals, pre-existing pulmonary disorders, chronic kidney disease, obesity, diabetes, hypertension and antecedent cardiovascular disorders. But to emphasize again, the vast majority of individuals recover uneventfully.

Why are there differences in the COVID and related mortality in different parts of the world?

As I noted above, with expanding data, the original 2-4% mortality from China is falling to an overall case fatality rate (CFR) of 1.4%. As you know, case fatality can be artificially high if only high-risk patients are being tested and if the numerator and denominator both require a positive test result for SARS-CoV2. Knowing that there is a larger population (and I don't think

we yet know how large it is) of individuals who have had an infection with SARS-CoV2 but who were either minimally symptomatic and didn't meet eligibility for testing (which has been stringent and limited even now) or whose mild symptoms or absence of symptoms never even raised the prospect of testing, the denominator of infected individuals may be larger than expected. In countries like Germany, where testing has been more available and where the mortality rate is less than other countries, this may help explain in part why the CFR is lower. But an additional factor could be where a country is in its infection, knowing that mortality can occur later in the infection, especially for patients admitted to ICU facilities. In contrast to Germany, Italy has reported a much higher CFA which can be related to its older demography and the fact that the exponential spread of infection strained an otherwise excellent medical systems to the point where medical care was limited and high risk individuals were unable to be cared for (which seems similar to what many are reporting in NYC and other areas with strained resources). But in Italy, as my Stanford colleagues Eran Bendavid and Jay Bhattacharya commented on in their March 24th opinion piece in the WSJ, a lack of true prevalence data could have inflated the CFR many-fold. This underscores the importance of knowing true prevalence data in order to better understand the overall disease severity and mortality – especially since that is mostly what is reported in the news media. As always, there is no substitute for good and reliable data.

Why are we getting different messages regarding the duration of the infection over the next months and year(s) and does the social distancing we are now doing make a difference?

I would bet that like you I have been intrigued as well as frustrated (and even horrified) by highly divergent modeling data – some of which have promoted recovery times that are truly discordant with the current reality and others, like the Imperial College modeling, that got a lot of attention when it forecast some 550,000 deaths for coronavirus and risk period of some 18 months that now seems flawed in some of its assumptions. We all recognize that it is imperative to have reliable assumptions that are ideally data based before doing modeling projections. I have noted previously, the best data we have to date is that the initially explosive infection that occurred in China took about three months to run its course, albeit with very rigorous mitigation through virtual lockdown. You will recall that it was from the state of Washington that on January 15th the first case of COVID was described in the US in an individual who had traveled from Wuhan, China. As the infection spread in the US, Washington became an initial hotspot and the first mortality was described at the Life Care Center in Kirkland where 19 deaths among elderly residents are attributed to SARS-Cov2. Gene sequencing of the virus demonstrated in Seattle that the virus had likely been circulating in the community in asymptomatic and mildly symptomatic individuals for weeks prior to the first reports of serious infection and death.

Because of concerns about the rapid spread of SARS-CoV2, different parts of the US have instituted varying degrees of social distancing or “shelter in place.” This really began in the six-county area in northern California (including Santa Clara and San Mateo counties) on March 16th and now includes 30 states, 81 counties, 15 cities and one territory and is a tribute to local community leaders, state Governors and other local leaders and officials. In fact, the leaders at Stanford were ahead of this curve, having instituted a university-wide shelter in place policy on March 13th. While confusion about how long these policies should continue emanated from the Executive Branch, most communities across the US have been paying attention to “bending the curve” – which really means spreading out the infection so as to not overwhelm medical care

resources as now seems to be unfolding in NYC. Because of the planning in California and at Stanford in particular, where many important decisions have been made, the capacity of ICU and related facilities could hopefully meet the needs of the community. By last week nearly 75% of medical encounters were happening by telemedicine, preparations had taken place to make more beds available to prepare for any surge that might occur, additional ICU beds were being recommissioned and countless other important decisions. This is a tribute to the leaders at Stanford Medicine, including the countless providers who are putting themselves on the line to care for others while risking getting infected themselves. And yes, Stanford too has experienced a lack of PPEs to protect its healthcare care workforce – which is another sad reality of our nation’s lack of preparedness.

While healthcare providers cannot shelter in place, many have children who are not in school and, unlike other scenarios, unable to be cared for by older grandparents. This raises important questions regarding provisional emergency childcare which has fallen off most radar screens – but not that of my wife, Peggy, who has worked in this area for many decades. She has been working tirelessly to help catalyze local and hopefully national policies that support babies and children as well as their parents who we count on to provide medical care. She wrote an opinion article about this that I am attaching for your information (https://www.paloaltoonline.com/news/2020/03/27/guest-opinion-navigating-the-storm-of-child-care-and-school-closures-during-the-pandemic?utm_source=express-2020-03-30&utm_medium=email&utm_campaign=express)

My colleagues at the Seattle Children’s Hospital indicated last Thursday that they were seeing early data suggesting that the spread of infection might be flattening. In the Bay Area there could be some preliminary data later this week recognizing that it takes at least two incubation periods (or in the case of SARS-CoV2 about 28 days) to fully assess the state of the pandemic. Because California began social distancing earlier than other parts of the US, it may see early benefits sooner. But it is important to recognize that we are still in a situation where we have a vulnerable population, protected by the first wave of social distancing, who could be at risk once the restrictions are lifted – especially if SARS-CoV2 is still in the community or resurfaces later in the year (as is usually the case for respiratory viruses). This has led some investigators, including a group at the Harvard T.H. Chan School of Public Health to posit that intermittent social distancing tracks to different thresholds of community infection. This model assumes that COVID will be a seasonal infection. And while it has a rationale behind it, it could be highly disruptive to have periodic requirements for more stringent social distancing.

Of course, this also begs the question of whether social distancing will have the desired benefit – although I would argue that we already have data from what happened in China and especially Taiwan. Another modeling study from Singapore that was published in the March 23rd online Lancet Infectious Disease compared what happens when quarantine, school closure alone or workplace distancing alone is compared to the combination of each of these interventions or none of them. This model is influenced by the proportion of asymptomatic to symptomatic individuals and also whether children are symptomatic. It demonstrates, however, a dramatic reduction of infections (727,000 when nothing is done to 50,000 when all three interventions are combined) but also suggests that variations on this approach, perhaps including the one recommended above, might be feasible if more surveillance data was available.

These and related approaches have just been codified in a thoughtful analysis by leaders at the American Enterprise Institute that includes Scott Gottlieb, Caitlin Rivers, Mark McClennan, Lauren Silvis and Crystal Watson that was published on March 28th (<https://www.aei.org/wp-content/uploads/2020/03/National-Coronavirus-Response-a-Road-Map-to-Recovering.pdf>) and that highlights many of the issues I have noted above, including the need for better surveillance data to assess spread, exposure and immunity along with the need for improvements in the state and local health care systems, public health infrastructure, case containment and adequate medical supplies and finally, the availability of therapies, prophylactic and preventive interventions. They divide their recommendations into:

- Phase I – Slow the Spread, which really means the social distancing now underway – and hopefully soon fully across the US
- Phase II – State-by-State Reopening which could mean schools and businesses but which early in the reopening could still mean some protection for higher risk individuals
- Phase III would mean lifting physical distancing based on the extent of immune protection of the broader community – which will hopefully be advanced with available vaccines and treatments
- Phase IV – Rebuilding readiness for the next pandemic – which I would argue should commence long before the current one is resolved. In the past as soon as the sense of urgency and severity declines, so has our preparedness. We can't risk repeating that approach.

There still are many unanswered questions, including how long it will take to not just flatten the curve but to bend it and then eliminate it. This depends on issues already discussed, including whether this coronavirus will have seasonality, whether it will return next winter (assuming it goes away before then), what percentage of the population will actually have been exposed and to what degree will that provide some herd immunity (assuming that prior infection protects against future episodes with the same virus) and when there are effective therapeutic and preventive interventions. Until then we stay the course.

How is our DCI Community dealing with the pandemic?

So, it looks like we will be continuing with shelter in place until the end of April – and likely beyond then. I am pleased to note how different DCI classes are seeking ways to engage with each other – and ideally provide connection and a sense of community. Last week the DCI 2018 Class had a Zoom event that involved nearly every member of the class and included a topical discussion – and opportunities for other dialogue among the community. This is wonderful and I am grateful to Mark Clapper for his leadership in facilitating these and other opportunities.

We will continue to find ways to reach out to our entire DCI Community. We are planning another Town Hall meeting early in April. Details about that will be forthcoming.

Till then be well. And if you need help or guidance, please reach out.

Phil